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CHEMICAL PROTECTION OF THE MOUSE AGAINST LEUKEMIA INDUCTION BY --ETC(U)
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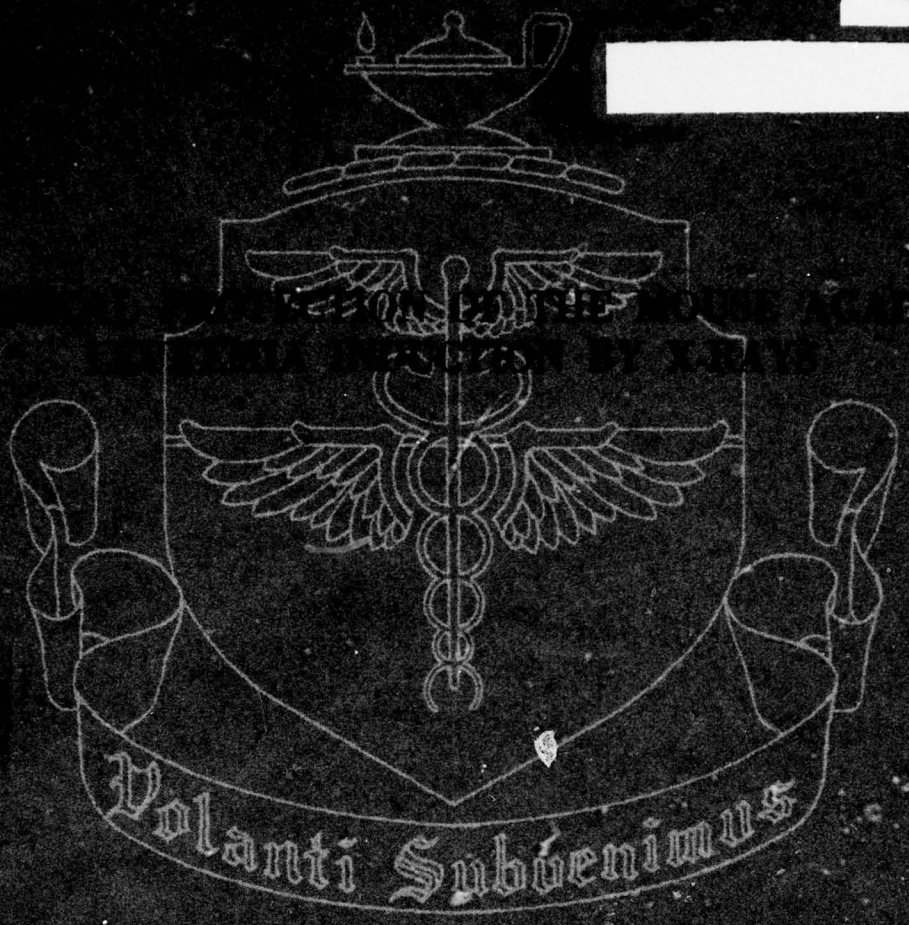
SCHOOL OF AVIATION MEDICINE
RANDOLPH AIR FORCE BASE, TEXAS

APRIL 1959



CHEMICAL PROTECTION OF THE MOUSE AGAINST LEUKEMIA INDUCTION BY X-RAYS

A major goal of the radiobiologist is the control of radiosensitivity. Encouraging progress toward this end has been made with the synthesis of mercaptoethylguanidine (MEG), a compound which enables mice to survive otherwise lethal x-ray doses (1). To ascertain whether this chemical protects against induction of leukemia by irradiation, mice were pretreated with the drug then given graded sublethal doses of x-rays. The incidence of leukemia in these animals was compared with that in similarly irradiated mice treated with saline placebos.

METHODS

Male mice of the RF strain aged 5 to 6 weeks were randomly divided into two groups. One group received intraperitoneally 9.0 mg. of freshly prepared MEG dissolved in 0.3 ml. of 0.4 M phosphate buffer at pH 7.0, and the other group received an equal volume of physiologic saline solution by the same route. About 15 minutes after injection, the animals were exposed to whole-body 250-kvp x-rays under conditions identical to those described previously (2) (table I). After irradiation, the mice, all of which survived at least 120 days, were caged in groups of 10 and observed until natural death. Postmortem examinations were performed on every animal, and histologic studies were made when necessary for diagnostic purposes.

RESULTS

In the placebo-treated mice, the incidence of thymic lymphoma and granulocytic leukemia was increased by irradiation (table I), in accordance with the results of earlier studies (3). In the MEG-treated mice, however, the induction of granulocytic leukemia was less pronounced at both dose levels, and the induction of thymic lymphoma was completely inhibited (fig. 1). Another noteworthy difference between the two irradiated groups was the longer survival of the MEG-treated mice. In the nonirradiated controls, MEG did not materially affect the survival or spontaneous development of neoplasms.

DISCUSSION

It was anticipated that MEG would reduce sensitivity to leukemia-induction in view of the protection it affords marrow cells against acute radiation injury in vivo (4) and in vitro (5) and because of the importance of marrow injury in the induction of lymphoma (6) and granulocytic leukemia (3). That it should be

TABLE I

Effects of MEG pretreatment on leukemia-induction by x-rays

X-ray dose (r)	Pretreatment	Number of mice	Mean survival time (months)	Leukemia incidence (%)	
				Granulocytic	Thymic lymphoma
0	Saline	69	19.6	4.4	4.4
0	MEG	43	20.0	6.9	2.3
150	Saline	50	16.9	26.0	6.0
150	MEG	68	18.4	19.1	7.4
300	Saline	59	14.2	40.7	20.3
300	MEG	59	15.0	35.6	6.8

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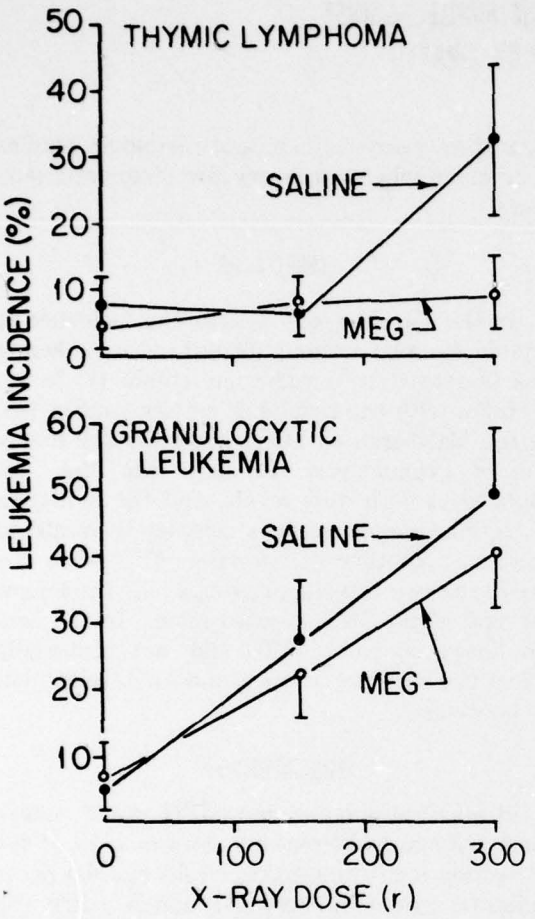

FIGURE 1

Leukemia incidence in relation to radiation dose in MEG- and saline-treated mice. The values shown, with their standard errors, represent the observed incidence after adjustment by the method of Kimball (13) to correct for intercurrent mortality from diseases other than leukemia.

especially effective in protecting against leukemia-induction was also suggested by the relatively high selective concentration of the drug in marrow and lymphoid cells, as judged from preliminary studies of the organ distribution of S^{35}-labeled MEG (F.P. Conte, G.S. Melville, Jr., E.E. Schwartz, D.G. Doherty, and R. Shapira, 1958, unpublished data).

Although the observed protection against leukemia-induction and life-shortening is not statistically significant because of the relatively few animals used, the results are in accord with those of earlier studies indicating protection by MEG against leukemogenesis and life-shortening in irradiated mice of the (101 x C3H)F_1 strain (7). A quantitative assessment of the extent of protection against leukemogenesis must, however, await studies with additional dose levels and large numbers of animals. In comparison, for protection against 30-day lethality (1) and bone marrow depression (4), MEG appears to reduce the effectiveness of x-rays by a factor of 2.0.

Our results, like those of our earlier experiments (table II) and those of Hollcroft et al. (8) indicate the feasibility of protecting animals against delayed radiation injury, as well as against acute lethality, by measures which may be applied before irradiation. Although preliminary clinical tests suggest that MEG may be too toxic for man to be of value in human protection, related agents have been synthesized that appear more promising for clinical use (D.G. Doherty, 1958, unpublished data).

The mechanism whereby MEG protects cells against the effects of ionizing radiation is not yet known. It is thought, however, that the major action of the drug is that of a radical-trapping agent within the cell (1). It is noteworthy that MEG also protects against the effects of nitrogen mustard (9).

Since the protective action of MEG is believed to be similar to that of cysteamine, it is paradoxic that the latter compound was not found to protect C57BL mice against induction of lymphomas by gamma rays (10). In the latter case, however, the radiation was given in two exposures 5 days apart; hence, in view of the complex interaction between dose, time, and radiation intensity in lymphoma-induction (11, 12), the dose-reducing action of cysteamine and cystamine might have modified the relation between dose and interval in such a way as to enhance, rather than reduce, the leukemogenic effectiveness of the radiation.

Other reports concerning the effects of radioprotective chemicals on radiocarcinogenesis are also difficult to evaluate (13). For example, Duplan (14) failed to note protection by polyphenol derivatives against lymphoma-induction in strain XVII mice; however, his observed

TABLE II

*Longevity and leukemia in irradiated (101 x C3H)F_1 mice treated with MEG and bone marrow**

X-ray dose (r)	Treatment†	Surviving 30 days		Median after survival‡ (months)	Life-shortening (%/r)	Leukemia§ (%)
		Number	Percent			
0	Control	110	100	25.5	0	0.09
700-800	None	116	58	15.5	0.052	5.2
1100-1200	Bone marrow	113	47	13.0	0.043	0
1300-1800	MEG	134	52	13.0	0.036	0.7
1600-1800	MEG, Bone marrow	110	43	12.0	0.031	0

*From G.E. Cosgrove, A.C. Upton, C.C. Congdon, D.G. Doherty, and A.W. Kimball, unpublished data, modified from A. Hollaender et al. (7).

†MEG, 8.8 mg. per mouse, administered intraperitoneally 10 minutes before irradiation. Isologous bone marrow cells, 1 femur-equivalent in Tyrode's solution, administered intravenously immediately after irradiation.

‡Mice were females, irradiated when 3 months old.

§Thymic lymphoma.

leukemia incidence was lower in nonprotected mice exposed to 600 r than in those exposed to 400 r, suggesting that the frequency of leukemia was inversely related to dose in this range. Hence the slightly higher incidence of leukemia observed in his treated mice may conceivably denote dose-reduction. Without further dose-response data, his results cannot be interpreted, nor will they be meaningful until verified statistically with larger numbers of animals. Similarly, preliminary data on the occurrence of radiation-induced neoplasms in rats treated with mercaptoethylamine (15) para-aminopropriophenone (16), and hypoxia (17) cannot be evaluated for evidence of dose-reduction without additional dose-response data from nonprotected irradiated controls and without allowances for differences in longevity between the various treatment groups.

In summary, the general effectiveness of radioprotective chemicals in inhibiting radiocarcinogenesis cannot be ascertained without considerably more information than is now available. Among the facts needed for a proper evaluation of this question are more complete data on the pharmacology, metabolism, anatomic distribution, and mode of action of the various radioprotective agents. For example, cysteamine, which decreases the yield of mutations in certain bacteria (18), increases their frequency in irradiated *Neurospora* (Kolmark, 1958, personal communication). Because of differences such as this, generalizations about protective efficacy cannot be made. It is to be hoped, therefore, that research on the action of radioprotective chemicals in cells and animals of diverse types will be intensified and that greater emphasis will be placed on their protective effects against cancer-induction and delayed radiation injury.

SUMMARY

Administration of mercaptoethylguanidine shortly before a single whole-body exposure to 150 or 300 r of x-rays inhibits the induction of granulocytic leukemia and prevents the induction of thymic lymphoma in RF mice.

Mice treated with the drug also exhibit less shortening of the life span by radiation than do untreated controls.

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